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Incidence of Hepatocellular Carcinoma According to Hepatitis B Virus Genotype in Alaska Native People

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Abstract

Background & Aims—Most regions of the world have <3 co-circulating hepatitis B virus (HBV) genotypes, which limits direct comparisons of hepatocellular carcinoma (HCC) risk among HBV-infected persons by genotype. We evaluated HCC incidence by HBV genotype in a cohort of Alaska Native (AN) persons where 5 HBV genotypes (A, B, C, D, F) have been identified.

Methods—Our cohort comprised AN persons with chronic HBV infection identified during 1983–2012 who consented to participate in the study. Cohort persons were offered annual hepatitis B e antigen (HBeAg) testing and semiannual HCC screening. We developed a logistic regression model to compare HCC risk by genotype, adjusting for age, sex, region, and HBeAg status.

Results—Among the 1,235 consenting study participants, 711 (57.6%) were male, 510 (41.3%) were HBeAg positive at cohort entry, and 43 (3.5%) developed HCC. The HBV genotype was known for 1,142 (92.5%) persons (13.5% A, 3.9% B, 6.7% C, 56.9% D, 19.0% F). The HCC incidence/1,000 person-years of follow-up for genotypes A, B, C, D, and F was 1.3, 0, 5.5, 0.4, and 4.2, respectively. Compared with persons with HBV genotype B/D infection, the HCC risk was higher for persons with genotypes A (adjusted odds ratio [aOR]: 3.9, 95% CI: 1.14–13.74), C (aOR: 16.3, 95% CI: 5.20–51.11), and F (aOR: 13.9, 95% CI: 5.30–36.69).

Conclusion—HBV genotype is independently associated with HCC risk. AN persons with genotypes A, C, and F are at higher risk compared with genotypes B or D.

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Keywords

liver cancer; risk factors; Native American; epidemiology; genomics

INTRODUCTION

An estimated 2 billion persons have been infected with hepatitis B virus (HBV) worldwide, and approximately 620,000 die annually from acute and chronic sequelae of HBV infection (1, 2). Roughly 350–400 million persons are also chronic carriers (3), and they are at increased risk of developing complications such as cirrhosis and hepatocellular carcinoma (HCC). The risk for experiencing liver-related complications associated with HBV infection is influenced by demographic, environmental, and viral factors (4).

The HBV genome is classified into eight genotypes (A through H) (5, 6). Multiple subtypes have also been identified (7). Specific HBV genotypes predominate by geographical region, with most regions containing only 2 or 3 co-circulating types (8). The risk for developing HBV-related liver disease varies by genotype (9). In Asia, for example, persons with HBV genotype C progress more rapidly to cirrhosis and HCC than persons with genotype B (10, 11). In Western Europe and North America, a higher association has been demonstrated between genotype D and HCC compared with genotype A (12). Few studies, however, directly compared HBV-associated outcomes by HBV genotype given the geographic segregation of the genotypes.

Alaska Native (AN) people have historically had some of the highest rates of HBV infection and HCC in the world (13). In a 1990 study of chronic HBV carriers among AN persons, the annual HCC incidence was 387/100,000 person-years for men and 63/100,000 person-years for women (14). AN people also represent the only non-immigrant population where 5 of the 8 HBV genotypes (A2, B6, C2, D2/D3, and F1) co-circulate (15). The present study describes the epidemiology of HCC and evaluates HCC incidence by HBV genotype in a population-based cohort of AN persons with chronic HBV infection where 5 genotypes (A, B, C, D, F) have been identified.

PARTICIPANTS AND METHODS

Data Source & Study Participants

This study is a retrospective analysis of data collected on a cohort of HBV-infected AN persons. From March 1983 until October 1986, a statewide vaccination program was conducted to reduce the burden of HBV in AN people (16). Approximately 54,000 AN persons, representing 84% of the statewide AN population, received serological screening for HBV infection as part of the vaccination campaign. Persons were initially screened for HBV infection by testing for hepatitis B core antibody. Persons testing positive for hepatitis B core antibody received confirmatory testing by screening for hepatitis B surface antigen (HBsAg). Individuals testing positive for HBsAg twice at least 6 months apart were defined as having chronic HBV infection. The number of HBV susceptible persons entering the AN population and the number of additional persons who were screened for HBV after 1986 are

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unknown. However, HBV infection is a reportable disease in Alaska, and the Alaska Native Tribal Health System has worked with the State of Alaska to link AN persons with HBV to healthcare.

All AN persons with chronic HBV infection identified during the vaccination campaign were entered into a clinical registry maintained by the Alaska Native Medical Center's Hepatitis Program to coordinate routine monitoring of their disease. In addition, all AN persons with HBV infection identified by statewide surveillance after the vaccination campaign were reported to the Hepatitis Program and added to the clinical registry. Persons in the chronic HBV registry were mailed reminder letters every 6 months to present to their clinical provider for a blood draw. The sera were tested for α-fetoprotein (AFP) semiannually and hepatitis B e antigen/antibody (HBeAg/Ab) annually. Beginning in 2001, HBV DNA was assessed at baseline and aminotransferase levels were assessed every 6 months. Testing for HBV DNA was repeated every 6–12 months for persons with a baseline HBV DNA level >2,000 IU/mL, a family history of HCC, or if aminotransferase levels were elevated.

For inclusion into our study, we selected participants from the clinical registry if they had a positive HBsAg test result after the start of the statewide vaccination campaign on March 1, 1983 and before December 31, 2012, the end of our study period. Out-of-state residents and non-AN persons were excluded from the study cohort.

Identifying Cohort Persons with HCC

Cohort persons with HCC were most commonly identified through HCC surveillance by the Hepatitis Program. The HCC surveillance program consisted of semiannual AFP screening for all persons in the HBV clinical registry. Persons with an elevated AFP (≥25 ng/mL during 1982–1992, ≥15 ng/mL beginning in 1993–1999, and ≥10 ng/ml after 2000) and persons at high risk for HCC (e.g., persons with a family history of HCC or cirrhosis) were referred for radiologic testing to evaluate for HCC. Pathologic confirmation of HCC was available for a subset of participants undergoing biopsy or tumor resection. For persons who declined further intervention, a clinical diagnosis of HCC was made according to prevailing guidelines (17) and in consultation with a hepatologist and radiologist. In addition, persons with HCC were identified by cross-referencing cohort participants with the Alaska Native Tumor Registry, a National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) program registry. The Alaska Native Tumor Registry HCC case identification and classification methods strictly follow SEER guidelines (18, 19). Finally, we queried death certificate data from the State of Alaska Bureau of Vital Statistics to identify cohort persons with HCC listed as a cause of death.

Laboratory Testing

Testing for hepatitis B core antibody and HBsAg was performed at the Alaska Native Medical Center clinical laboratory using enzyme-linked immunoassay (Abbott Laboratories, Irving, TX) (16). Sera were tested for HBeAg by either enzyme-linked immunoassay (Abbott Laboratories, Irving, TX) or using the One-Step Hepatitis B e Antigen Test Strip (Abbott Laboratories, Irving, TX) and for anti-HBe using the Maxi:Test Anti-HBe Rapid

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Test (IND Diagnostic Inc. Delta, British Columbia, Canada). Testing for AFP was done by enzyme-linked immunoassay.

Using stored sera, study participants were genotyped by PCR and direct sequencing of the S gene. DNA extraction, nested PCR, DNA sequencing, and genotyping were performed as previously described (15, 20).

Residential Status

Residential status was defined based on the location where a person received healthcare at the time of diagnosis. The majority of participants resided in one of five healthcare service regions. To protect participant confidentiality, we refer to these healthcare service regions as Regions A, B, C, D, and E. Participants outside these five healthcare service regions were grouped into an Other Regions category. Region A is in southcentral Alaska, Regions B and C are in southwest Alaska, and Regions D and E are in northwest Alaska. Region A is considered more urban compared with Regions B–E, which are predominantly rural.

Statistical Analysis

We defined HCC incidence as the number of confirmed HCC diagnoses per 1,000 person-years of follow-up. Person-years of follow-up is the date of the first HBsAg positive test after 3/1/1983 until HCC diagnosis, death, or the end of study period on 12/31/2012. We developed univariate logistic regression models to evaluate risk factors for HCC among cohort participants, and a multivariate model to compare HCC risk by genotype, controlling for age at study entry, sex, region, and initial HBeAg status (defined as the first HBeAg result after cohort entry). Wald p-values representing the combined significance across all levels of a variable are provided. Statistical analyses were conducted using SAS version 9.3 software (SAS Institute Inc., Cary, NC).

Human Subjects Review

This study was approved by institutional review boards of the Alaska Area Indian Health Services and the CDC in Atlanta, Georgia, and by the Alaska Native Tribal Health Consortium, the Southcentral Foundation, and the Yukon-Kuskokwim Health Corporation. Informed consent was obtained from all living participants for storage of sera and future laboratory testing of HBV seromarkers and HBV DNA. Information for deceased participants was used with institutional review board permission.

RESULTS

Study Population Characteristics

Among the 1,535 persons entering the chronic HBV registry from March 1983 to December 2012, 1,268 (83%) consented for inclusion into the study cohort (Figure 1). We excluded 32 out-of-state residents and 1 non-AN person. Of the 1,235 AN persons with chronic HBV-infection included in the final study population, 1,137 were identified during the vaccination campaign (1983–1986) and 98 were identified through statewide HBV surveillance and added to the Hepatitis Program’s clinical registry.

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In the final study population, 711 (58%) participants were male (Table 1). The majority of participants lived in Region A (36%) or Region C (37%) at the time of HBV diagnosis. The initial serologic test for HBeAg was positive in 510 (41%) participants. HCC was diagnosed in 43 (3.5%) participants. Most participants with HCC were male (70%), HBeAg positive (56%) on their initial serologic test, and resided in the Region A (33%) or C (37%).

Description of Study Cohort by Genotype

The HBV genotype was unknown for 93 participants in the final study population. Among participants with a known genotype, 57% were infected with HBV genotype D followed by genotypes F (19%), A (13%), C (7%), and B (4%) (Table 1). These genotypes were represented by subtypes D2/D3, F1, A2, C2, and B6, respectively. No other subtypes circulated in Alaska. Also, no evidence of mixed HBV genotype infections was detected. Median age of entry into the study cohort was 25.9 years, ranging from 17.6 years for participants with HBV genotype F to 52.5 years for participants with genotype B (Table 2). Of the 346 deaths that were observed, 185 (54%) deaths occurred in participants with genotype D and 64 (19%) among participants with genotype F. Overall, the median age at death was 56.4 years, ranging from 39.9 years for genotype F to 77.4 years for genotype B. Of the 43 HCC cases observed in the cohort, 22 (51%) occurred in participants with genotype F and 10 (23%) in participants with genotype C. Genotype B was not found in any of the participants with HCC. The median age at HCC diagnosis was 44.7 years, ranging from 23.0 years for genotype F to 59.8 years for genotype A. Study participants were observed for a total of 27,729 person-years of follow-up, or a median of 29.1 years/person.

Geographic Distribution of HBV Genotypes

The majority of HBV cases were attributable to a predominant genotype in most regions of Alaska (Figure 2). In Region A (67%), Region B (89%), and Other Regions (49%), genotype D accounted for the majority of HBV infections. In Region E, the majority of infections were genotype C (65%), and in Region D, more than half of infections were genotype F (58%). In Region C, the predominant genotype was D (48%), although genotypes A (22%) and F (22%) also accounted for a large share of infections.

Risk for Developing HCC among HBV-Infected Persons

In the multivariate analysis, age ($p=0.02$) and HBV genotype ($p<0.01$) were associated with HCC (Table 3). HCC risk was higher for participants aged ≥60 years (adjusted odds ratio [aOR]: 3.8; 95% confidence interval [CI]: 1.25–11.46) compared with participants aged <40 years, and higher among participants with genotypes A (aOR: 3.9, 95% CI: 1.14–13.74), C (aOR: 16.3, 95% CI: 5.20–51.11), and F (aOR: 13.9, 95% CI: 5.30–36.69) compared with participants infected with genotypes B or D. Male sex, area of residence, and HBeAg status were not associated with risk of HCC in the multivariate model.

DISCUSSION

In this study, we compared the epidemiology of HBV infection and the risk of developing HCC by 5 genotypes (A2, B6, C2, D2 and D3, and F1) in a cohort of AN persons. Genotype was the strongest risk factor for developing HCC and explains the geographical differences

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in observed HCC rates. Overall, the highest prevalence of HCC occurred in Regions C, D, and E, reflecting the higher proportion of genotypes C and F in these areas. The lowest HCC prevalence occurred in Region B where genotype D was found in over 80% of infected persons.

The present study confirmed our previously reported association between HCC and genotype F (aOR: 11.7, 95% CI: 5.4–25.4) and other genotypes in a nested case-control study in this population, adjusted for region, sex, and birth cohort (15). HBV genotype F is also found in indigenous populations in Central and South America, and it is divided into four subtypes (F1–F4) (21, 22). Subtype F1 is represented in the AN population. Studies of genotype F, however, are limited and little is known regarding the clinical outcome of these infections. Potentially, the high risk of HCC associated with genotype F may be explained by specific viral mutations. Prior investigations implicated a basal core promotor double mutation (T1762/A1764) with upregulation of HBV expression and increased virulence and progression to HCC (23, 24). Although no significant association was found previously in this cohort between HCC and mutations in the basal core promoter or pre-core regions of genotype F (15), this genotype might affect the development of HCC through an as yet unidentified molecular mechanism. Follow-up studies may consider a genome-wide search for unique mutations in AN persons as well as mutations in the viral genome, or possible differences in the integration patterns for genotype F in the host hepatocyte DNA compared with other HBV genotypes.

Our study also confirmed the well-described association between HBV genotype C and HCC. Genotype C can be divided into 4 subgenotypes (C1, C2, C3, C4) (25–27). Genotype C2, the subgenotype found in Alaska, can also be found in China (28) and Western Siberia. A possible reason for the association between HBV genotype C and HCC could be that participants with genotype C do not seroconvert from HBeAg to anti-HBe on average until the fifth decade of life, as opposed to a median age at seroconversion of less than 20 years for the other four genotypes found in Alaska (20). In Asia, both HBeAg and high levels of HBV DNA have been found to be significant risk factors for liver-related complications including liver inflammation, cirrhosis, and HCC (29, 30). Certain mutations such as the basal core promotor mutation, which are independently associated with HCC in studies from Asia, also appear to occur more frequently in those infected with genotype C2 (10, 31).

None of the 45 persons with HBV subgenotype B6 infection developed HCC during the study period. Given the small population size of persons with HBV subgenotype B6 in our cohort, we are unable to make generalizable statements about subgenotype B6 and HCC risk. However, studies among Canadian Inuit people with HBV infection have demonstrated that subgenotype B6 is infrequently associated with liver-related disease (32). In addition, phylogenetic analysis revealed that HBV subgenotype B6 is closely related to subgenotype B1, which is found predominantly in Japan (33). HBV genotype B1 is associated with a lower risk for HCC and HCC tends to occur later in life (9). A previous analysis revealed that persons with HBV subgenotype B6 infection in Alaska, Canada, and Greenland had similar clinical characteristics to persons with subgenotype B1 infection from Japan (33). Thus, we would expect that AN persons with HBV subgenotype B6 in our cohort would be at low risk for liver-related disease.

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Several limitations of the current analysis warrant discussion. First, this study is a retrospective cohort analysis. Inherent with any retrospective study design using existing medical record data is the inability to collect and review data on other, previously unidentified potential confounders. Furthermore, our analysis was confined to data included in the HBV clinical registry. The registry was not intended to be a comprehensive clinical record so we lacked complete information on HCC risk factors for persons not developing HCC, such as family history of HCC, presence of cirrhosis, diabetes mellitus, alcohol abuse, hepatitis C virus coinfection, and human immunodeficiency virus coinfection (hepatitis D virus infection has not been reported in AN people). The potential confounding effects of these factors may partially account for the associations between other risk factors and HCC observed in our analysis. In addition, it is unknown how many HBV susceptible persons entered the AN population after the vaccination campaign. However, the Alaska Native health system initiated universal infant HBV vaccination in 1984 and achieved 99% coverage among children aged 19–35 months by the 1997 National Immunization Survey (34). Consequently, we expect that very few persons in the AN population were HBV susceptible following the vaccination campaign and that the majority of HBV-infected AN persons are included in our cohort. Finally, the study's findings are derived from a sample of people based in Alaska who are exclusively AN. Differences in the socioeconomic, demographic, and biological characteristics of this population may mean that our results are not generalizable to other populations.

Several strengths of the current analysis also deserve discussion. First, our study approximates a population-based cohort because 84% of the AN population was screened for HBV infection during the vaccination campaign. The implementation of a universal infant HBV vaccination program reduced the population of HBV susceptible persons after the campaign (34). Any HBV susceptible AN persons diagnosed with HBV infection after the vaccination campaign were reported to the Alaska Native health system by the State of Alaska. Second, we attempted to identify all HCC cases among consenting cohort participants by searching multiple data sources (HBV clinical registry, the Alaska Native Tumor Registry, and State of Alaska vital statistics data), which permitted calculating comprehensive incidence rates. Third, this study is the first to examine the incidence of HCC in genotypes A2, B6, C2, D2/D3 and F1 in a population-based cohort. Finally, we have more than 25 years of follow-up on the majority of participants which provided adequate time to study the natural history of disease and capture most cases of HCC.

The evidence available suggests that HBV genotype is an independent risk factor for HCC. Further prospective follow-up, as well as molecular examinations of full HBV genome sequences and host immune responses, are needed to define these relationships. Future HCC surveillance programs should consider including viral genotype in risk stratification. The contribution of genotype and other viral characteristics may very well be important in devising HCC surveillance strategies and treatment plans. Although aggressive and ongoing monitoring is recommended for all HBV genotypes, persons infected with C and F, as well as genotype A, may require earlier (and more frequent) monitoring to reduce lifetime risk of developing HCC. Furthermore, current guidelines only recommend HCC surveillance for HBV carriers who are Asian men older than age 40 and Asian women older than age 50, persons with cirrhosis, persons with a family history of HCC, first-generation African

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Americans older than age 20, and any carrier older than age 40 with persistent or intermittent ALT increases and/or HBV DNA levels greater than 2000 IU/mL (17). Surveillance may need to be considered for young adults in their late adolescence to early 20s given the young median age among persons with genotype F at HCC diagnosis. Continued follow-up of the AN population is needed, as well as investigational inquiries into the role that genotype may play in influencing other disease manifestations and response to antiviral treatment.

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List of Abbreviations (in order of appearance)

HBV	hepatitis B virus
HCC	hepatocellular carcinoma
AN	Alaska Native
HBeAg	hepatitis B e antigen
aOR	adjusted odds ratio
HBsAg	hepatitis B surface antigen
AFP	α-fetoprotein
HBeAb	hepatitis B e antibody
SEER	Surveillance, Epidemiology, and End Results Program
YKD	Yukon-Kuskokwim Delta
CI	confidence interval

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Key points

- Most studies evaluating hepatocellular carcinoma (HCC) risk in hepatitis B virus (HBV) infected persons included ≤3 genotypes.
- We evaluated the HCC incidence in a population-based cohort of HBV-infected AN persons followed for up to 30 years.
- Our study uniquely allowed for direct comparison of HCC risk by 5 HBV genotypes (A, B, C, D, F) after adjusting for age, sex, region, and HBeAg status.
- We demonstrated that HBV genotype is independently associated with HCC risk; persons with HBV genotypes C and F are at highest risk.

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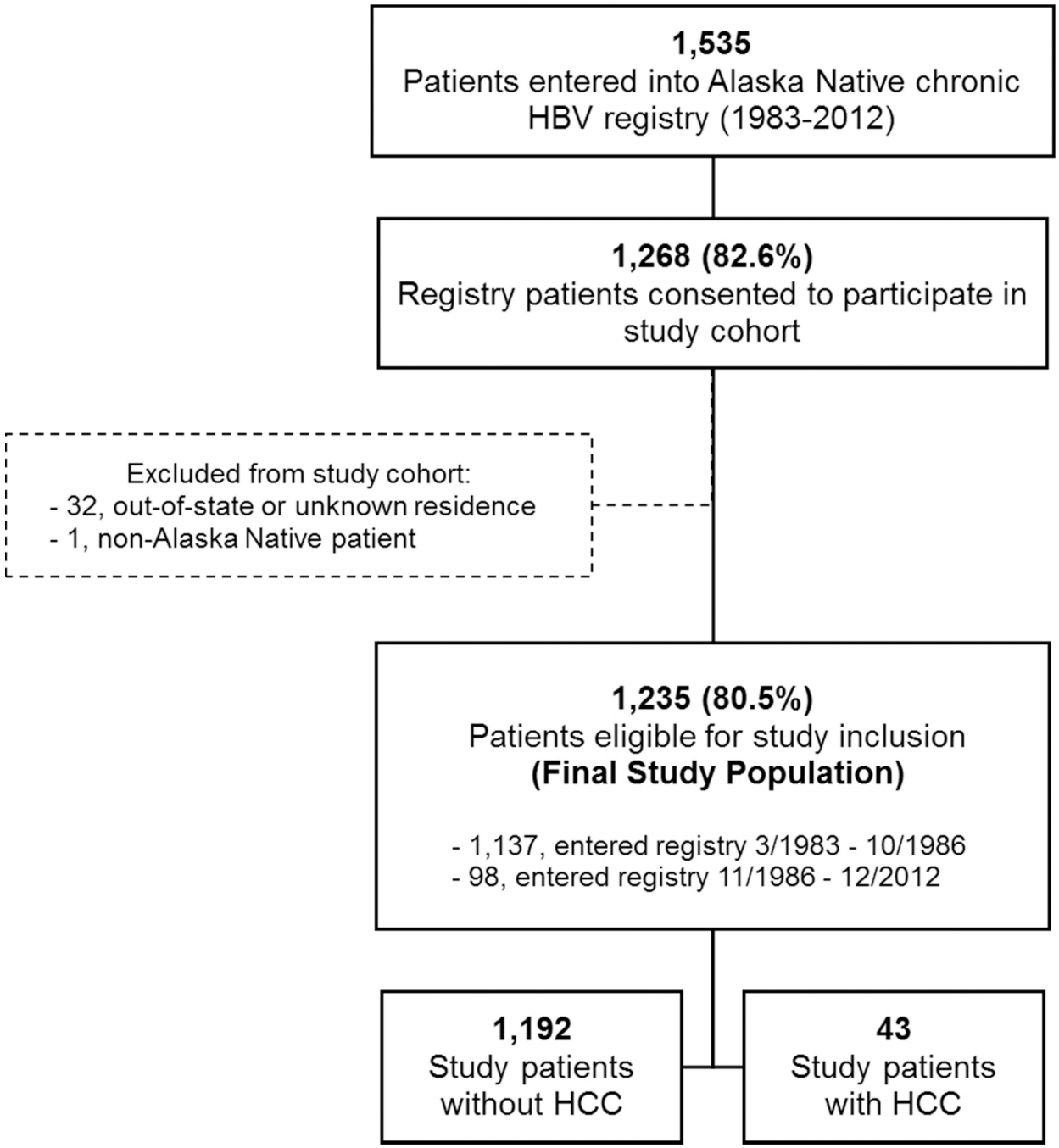

Figure 1.

Study population of persons with chronic hepatitis B virus (HBV) infection (Alaska, 1983–2012).

Abbreviation: HCC, hepatocellular carcinoma

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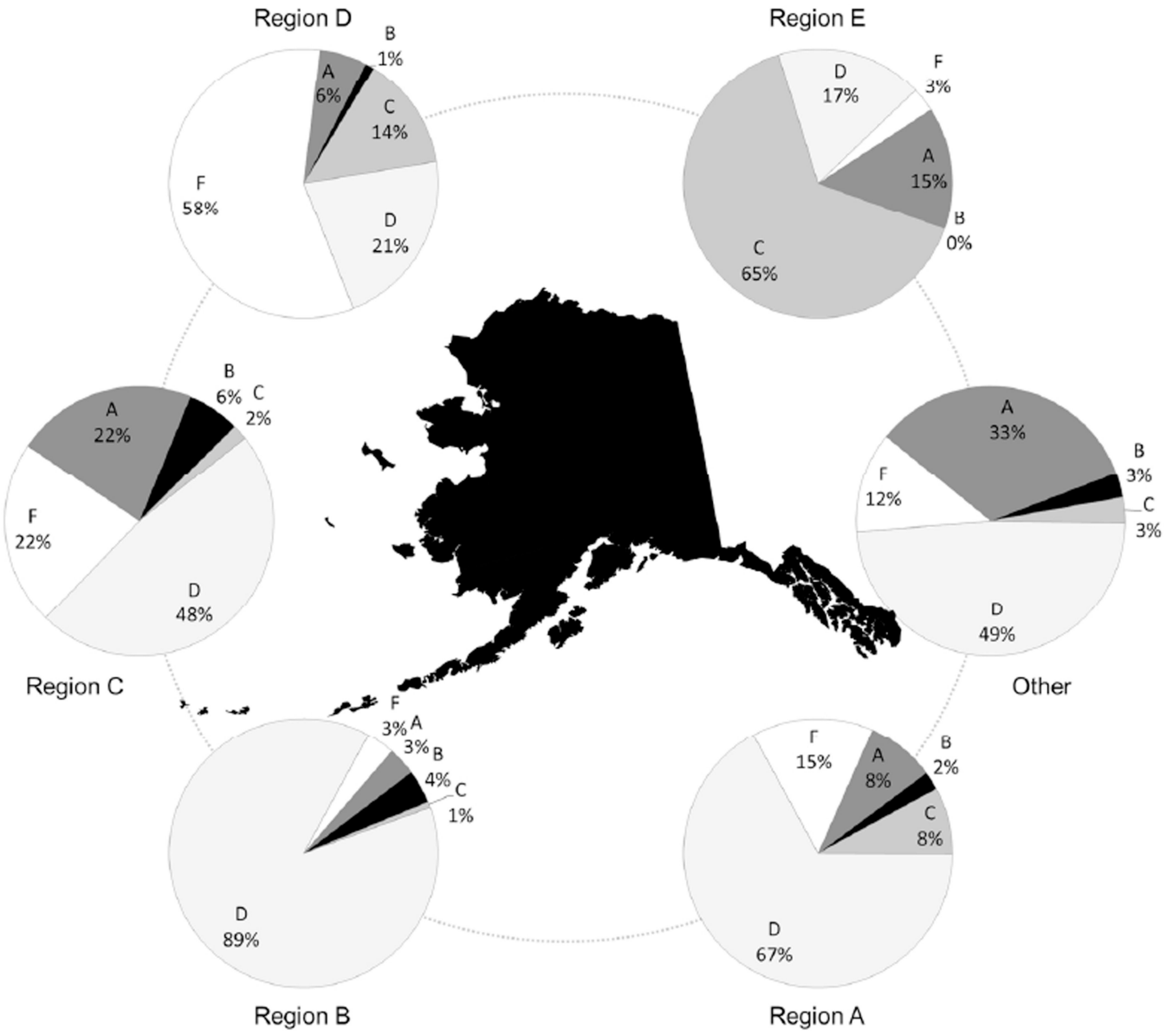

Figure 2.

Geographic distribution of HBV genotypes (Alaska, 1983–2012).

Note: Proportions were determined excluding cases with unknown or missing HBV genotype.

Abbreviations: HBV, hepatitis B virus.

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Table 1

Characteristics of a cohort of Alaska Native persons with chronic HBV infection – Alaska, 1983–2012

Characteristics	Number with HBV	Number with HCC	HCC Incidence*
	Total (%)	Yes (%)	
Total	**1235**	**43**	
Sex			
Female	524 (42.4%)	13 (30.2%)	1.0
Male	711 (57.6%)	30 (69.8%)	1.8
HBV Genotype§			
A	154 (13.5%)	5 (11.6%)	1.3
B	45 (3.9%)	0 (0%)	0
C	76 (6.7%)	10 (23.3%)	5.5
D	650 (56.9%)	6 (14.0%)	0.4
F	217 (19.0%)	22 (51.2%)	4.2
Unknown/missing genotype	93†	0	--
Region			
Region A	444 (36.0%)	14 (32.6%)	1.3
Region B	161 (13.0%)	1 (2.3%)	0.3
Region C	463 (37.5%)	16 (37.2%)	1.4
Region D	94 (7.6%)	7 (16.3%)	3.4
Region E	34 (2.8%)	3 (7.0%)	3.6
Other	39 (3.2%)	2 (4.7%)	2.4
HBeAg Status (first test)			
Negative	725 (58.7%)	19 (44.2%)	1.1
Positive	510 (41.3%)	24 (55.8%)	1.9

Abbreviations: HBV, hepatitis B virus; HCC, hepatocellular carcinoma; nd, not determined.

*HCC rate/1000 person-years of follow-up.

†Column percentages exclude unknown/missing subjects.

§HBV is represented by subtypes A2, B6, C2, D2/D3, and F1. No other subtypes currently circulate in Alaska.

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Table 2

Demographic characteristics, clinical outcomes, and person-years of follow-up of Alaska Native persons with chronic HBV infection by genotype – Alaska, 1983–2012

Characteristics	Genotype*					
	A	B	C	D	F	Overall†
Number of participants	154	45	74	650	217	1142
Median age at study entry (IQR)§	24.5 (17–35)	52.5 (37–59)	24.2 (15–45)	21.2 (9–35)	17.6 (11–28)	25.9 (11–36)
Number male (%)	94 (61.0%)	24 (53.3%)	35 (46.1%)	369 (56.8%)	132 (60.8%)	654 (57.3%)
Number alive at end of study period¶	110	19	49	465	153	796
Median age of survivors (IQR)	50.7 (45–58)	62.7 (53–80)	48.3 (41–58)	45.1 (36–56)	45.2 (39–54)	47.1 (38–57)
Number died during study period	44	26	27	185	64	346
Median age at death (IQR)	53.5 (39–72)	77.4 (69–81)	61.9 (44–72)	56.4 (35–72)	39.9 (29–60)	56.4 (36–72)
Number with HCC during study period	5	0	10	6	22	43
Median age at HCC diagnosis (IQR)	59.8 (44–76)	--	59.2 (46–67)	54.2 (45–78)	23.0 (18–40)	44.7 (22–61)
Total person years of follow-up **	3883.7	916.5	1812.6	15933.0	5183.0	27728.8
Median (IQR)	29.1 (25–30)	20.6 (15–29)	27.0 (20–29)	29.1 (23–29)	29.8 (18–30)	29.1 (21–30)

Abbreviations: HBV, hepatitis B virus; HCC, hepatocellular carcinoma; IQR, interquartile range.

*HBV is represented by subtypes A2, B6, C2, D2/D3, and F1. No other subtypes currently circulate in Alaska.

†Overall includes persons with known genotype.

§Entry into study is 3/1/1983 or date of first HBsAg positive test, whichever is later.

¶End of study is 12/31/2012.

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** Person years of follow-up are from entry into study to HCC diagnosis, death or end of study period on 12/31/2012.

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Table 3

Odds ratios for various characteristics of study participants with HCC – Alaska, 1983–2012

Characteristic	Crude OR	95% CI	P-value	Adjusted OR*	95% CI	P-value
Age Group†						
<40 years	1.0	Ref	0.19	1.0	Ref	0.02
40–60 years	1.8	0.86–3.97		2.5	1.07–5.78	
≥60 years	1.8	0.69–4.84		3.8	1.25–11.46	
Age§	1.1	0.96–1.29	0.16			
Sex						
Female	1.0	Ref	0.10	1.0	Ref	0.09
Male	1.7	0.89–3.35		1.8	0.92–3.70	
HBV Genotype						
B/D¶	1.0	Ref	<0.01	1.0	Ref	<0.01
A	4.4	1.32–14.50		3.9	1.14–13.74	
C	19.7	6.96–56.01		16.3	5.20–51.11	
F	14.7	5.89–36.80		13.9	5.30–36.69	
Region						
Region A	5.2	0.68–39.90		2.5	0.30–21.07	
Region B	1.0	Ref	0.04	1.0	Ref	0.85
Region C	5.7	0.75–43.50		2.2	0.26–18.03	
Region D	12.9	1.56–106.01		1.9	0.21–17.88	
Region E	15.5	1.56–154.01		2.4	0.20–28.19	
Other	8.6	0.76–97.90		5.1	0.40–66.03	
HBeAg Status						
Negative	1.0	Ref		1.0	Ref	0.13
Positive	1.8	0.99–3.34	0.05	1.7	0.86–3.40	

Abbreviations: CI, confidence interval; HBeAg, hepatitis B E Antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; OR, odds ratio; Ref, referent group.

*Adjusted for age, sex, genotype, and region, excluding cases with unknown genotype.

†Age group is age at entry into study.

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§ Age as a continuous variable by 10 year increments.

¶ Referent group includes genotypes B and D.